TITLE PAGE

Pendular Seesaw Nystagmus in a Patient with a Giant Pituitary Macroadenoma: Pathophysiology and the Role of the Accessory Optic System

(Running Title: Pendular Seesaw Nystagmus Pathophysiology and the Accessory Optic System)

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Conflict of Interest Statement

No work resembling the enclosed article has been published or is being submitted for publication elsewhere. We certify that we have each made a substantial contribution so as to qualify for authorship and that we have approved the contents. We have disclosed that there is no financial support for this work or other potential conflicts of interests.

Keywords

Seesaw nystagmus; pituitary macroadenoma; accessory optic system, vestibulo-ocular reflex

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ABSTRACT

Seesaw nystagmus is characterized by cyclic eye movement with a conjugate torsional component and a dissociated vertical component. In the first half of the cycle, one eye elevates and intorts while the other eye depresses and extorts. The pattern is reversed in the remaining half of the cycle. We report a case of pendular seesaw nystagmus in a patient with a giant pituitary macroadenoma. Disturbance in the visuo-vestibular system is postulated to contribute to this form of seesaw nystagmus. Lesions compressing the optic chiasm and the accessory optic system could interrupt the transmission of retinal error signals to the inferior olivary nucleus and the interstitial nucleus of Cajal, thus interfering with the adaptive mechanism of the vestibulo-ocular reflex and leading to pendular seesaw nystagmus.

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~~A 55-year-old female was admitted for progressive drowsiness and headache over one month. Three months before admission, she began to develop oscillopsia and blurring of vision. Neuro-ophthalmic examination showed reduced bilateral visual acuity to 6/60 (Snellen reading chart), bitemporal hemianopia and bilateral optic~~

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Introduction

Seesaw nystagmus (SSN) is a rare ocular phenomenon characterized by the cyclic movement of the eyes with two discrete elements, namely a conjunctive torsional and dissociated vertical component. In the first half of the cycle, intorsion and elevation are observed in one eye while extorsion and depression occurs in the other. The movement pattern is reversed in the remaining half of the cycle. Nystagmography studies have classified this peculiar sign as exhibiting either a pendular waveform or a jerky waveform (1-5). It is a rare ocular sign with only 50

cases reported in the literature. We report a case of SSN in a patient with a giant pituitary macroadenoma and discuss the possible pathophysiology.

Case Presentation

A 55-year-old Chinese female was admitted for progressive drowsiness and headache for one month. Three months prior to admission, she experienced oscillopsia and blurring of vision. On admission, the patient was ~~conscious and~~ alert ~~and was eupituitaric. There was~~ with reduced bilateral visual acuity to 6/60 with bitemporal hemianopia. Fundoscopy showed bilateral band optic atrophy compatible with a chiasmatic or tract lesion. The most striking feature was the presence of pendular-waveform seesaw nystagmus characterized by elevation with incyclotorsion in one eye and depression with excyclotorsion (counter-clockwise torsion) of the fellow eye in all gaze positions (see video). The vertical and rotatory oscillations continuously alternated with each eye in the absence of a fast phase. There was ~~no exacerbation of symptoms with head movement and there was~~ neither oculomotor nor abducens nerve palsy. There were also no signs of vestibular disturbance.

Serum thyroid-stimulating hormone (TSH), free thyroxine (T4), morning cortisol and prolactin levels were all within normal limits. Magnetic resonance imaging (MRI) depicted a giant pituitary tumor (5.8cm (height) x 5.7cm 9 (width) x 6.3cm (length)) in size (Fig. 1). The lesion extended into the parasellar region and encased the cavernous segment of the right internal carotid artery (Knosp-Steiner

grade IV). Superiorly, the lesion compressed against the optic chiasm and anterior third ventricle causing obstructive hydrocephalus. It also abutted the right meso-diencephalic junction.

Craniotomy and near total excision of the pituitary tumor was performed via the anterior interhemispheric transcallosal approach. The histopathological diagnosis was a non-functional pituitary adenoma. The patient's visual acuity did not show significant improvement and her bitemporal hemianopia as well as nystagmus persisted six-months after the procedure.

Discussion

The term SSN was first coined by Maddox in 1914 when he observed a patient with involuntary seesaw-like eye movements and bitemporal hemianopia ~~ of unknown origin~~ (6). ~~Although the pathogenesis of SSN remains elusive, c~~Two distinct forms of SSN exist, exhibiting either a jerky or pendular movement waveform. Jerky SSN, also known as hemi-SSN, consists of slow torsional phases in one direction (a~~one~~ half-cycle) and quick phases in the opposite direction for

the remaining half-cycle. In contrast, p~~P~~endular SSN ~~instead~~ describes a slow smooth oscillating ocular rolling movement (7). Ascertaining the ~~It is believed that the precise~~ pattern of SSN ~~can~~ may ~~describe~~ indicate the location of the lesion and offers insights on the complex interaction of the mechanisms involved in gaze stability.

Pendular SSN~~. Such patients are~~ is typically observed in patients such as ours diagnosed with tumors of the parasellar region with compression of the optic chiasm (1, 8)~~ (8)~~. Other etiologies include chiasm trauma, congenital achiasma and methotrexate-induced optic demyelination (4, 9-12). The resulting characteristic visual signs of optic chiasm compression, i.e. bitemporal hemianopia, ~~–~~are therefore frequently ~~observed~~ associated with ~~pendular~~ this form of nystagmus (5, 13). ~~In one case a resolution of SSN occurred following the recovery of bitemporal hemianopia (8).~~

Although the pathogenesis of pendular SSN remains elusive, Nakada et al theorized that dysfunction of the visuovestibular mechanisms that control eye movement may play a pivotal role (5). Physiologically the vestibulo-ocular reflex (VOR) ~~has a rotational component~~is elicited~~,~~ when the head rotates around a~~ny~~ cardinal axis (pitch, yaw or roll) with the purpose of stabilizing images on the retina. Vestibular detection of a change in head position generates simultaneous stimulatory and inhibitory signals to the extra-ocular muscles to induce reciprocal ocular counter-rotation about the same axis~~ed by ocular counter rolling about the same axis~~. Although ~~eliciting~~ triggering t~~t~~he reflex does not require visual input,

subcortical visuovestibular adaptive mechanisms are thought to exist to minimize an overshoot of ocular counter-rotation activity (5, 14, 15). One such subcortical mechanism involves the accessory optic system (AOS) that detects optokinetic stimuli through direction-selective retinal ganglion cells (15-17). This allows the AOS, that does not serve formed vision, to sense frame shift changes which can lead to corrective eye movements after signal processing through the cerebellum. During head movement ~~it regulated byr~~retinal error (known as retinal slip) signals are conveyed through the AOS ~~through the optic chiasm~~ to the inferior olivary nucleus (ION) which projects climbing fibers to~~and subsequently~~ the ~~inhibitory cerebellar~~floccular Purkinje cells of the cerebellum ~~flocculonodular lobe~~ (Figure 2) (5, 14, 15). Purkinje cells have been shown to transmit inhibitory signals to the vestibular nuclei and are critical in mediating the VOR adaptive properties of the AOS (5, 15, 18).

Nakada et al proposed that interruption of retinal error signals ~~at the level of the optic chiasm could~~could lead to a disinhibited VOR, independent of head movement, and may be the underlying mechanism for pendular SSN (5). The torsional component of the nystagmus was hypothesized to be due to an absence of visual information from the temporal visual fields due to chiasm compression with subsequent disruption of eye movement calibrations in the roll plane (5). But given the rarity of pendular SSN in patients with bitemporal hemianopia secondary to pituitary tumors, other pathogenic mechanisms need to be considered. We propose a complimentary hypothesis that requires the additional interruption

of internuclear signals of the AOS and the preservation of the interstitial nucleus of Cajal (INC), with its efferent projections, in order for pendular SSN to occur.

To elucidate the pathophysiology behind the dissociated vertical oscillations (in the pitch plane) that are the hallmark of pendular SSN, further understanding of AOS anatomy is required ~~We propose tha~~(14, 17, 19)~~.~~. Three paired AOS terminal midbrain nuclei receive visual signals from the contralateral retina through fibers of the ~~transpeduncular optic tract (also known as the~~ accessory optic tract~~)~~ that are then relayed to the ipsilateral ION (14-16, 19). Rabbit electrical microstimulation studies have revealed that each pair of AOS terminal nuclei processes visual information regarding one of three cardinal rotational axes (14). In particular, the medial~~-~~ terminal ~~nucleus~~ nucleus (MTN) ~~) of the AOS~~ processes retinal error signals in the pitch plane (14, 15)~~. and~~ The MTN is anatomically located at the ventral midbrain ~~tegmentum~~, bordered laterally by the cerebral peduncle and in close proximity to the interpeduncular cistern (19) ~~and medially by the mammillary bodies~~. ~~is particular~~Of the three terminal nuclei of the AOS, the MTN is the most vulnerable to anterior compression by ~~extremely~~ large suprasellar lesions as suggested by our case ~~as in our case~~ (Figures 1 and 2). The consequence of selective compression of the MTN could result in a lack of transmission of retinal frame shift error signals in the pitch plane leading to vertical nystagmus. The sparing of the more posteriorly located dorsal and lateral terminal nuclei at the pretectal region may explain why pendular SSN lacks a horizontal movement component.

The INC, located at the dorsomedial midbrain tegmentum, is an important constituent of the "eye movement neural integrator", a distributed network of neurons that combines ocular velocity signals and encodes them into position commands (18). In particular, the INC is believed to be responsible for generating vertical and torsional eye position signals and has extensive afferent and efferent pathways to the vestibular nuclei that are conveyed via the medial longitudinal fasciculus (7, 18, 20). Gamma aminobutyric acid (GABA) is a major inhibitory neurotransmitter of the central nervous system and GABAergic neurons were discovered to be predominantly active in governing AOS internuclear signaling relative to excitatory stimulation (15). Injury to the MTN could lead to disinhibition of the INC and several reports have emphasized the importance of its preservation for pendular SSN to develop (4, 5, 7, 21). Stereotactic lesioning of the INC in a patient was observed to abolish pendular SSN while electric stimulation evoked its exacerbation (7). Our hypothesis is supported by our patient's MRI findings that confirm not only the integrity of the posteriorly located INC, but also revealed considerable tumor compression of the optic chiasm and the anterior interpeduncular region of the midbrain.

Although an elucidation for the presence of the 180° out-of-phase dissociated vertical eye movement observed in pendular SSN is lacking, a phylogenetic theory has been suggested. Deregulation of the AOS with subsequent disinhibition of the INC could represent an unmasking of an atavistic VOR pathway mediating vertical eye movement observed in lateral-eyed animals (17). Lateral-eyed animals (in contrast to frontal in humans) normally have dissociated binocular vision, i.e.

when the head is tilted in the roll plane, one eye is turned superiorly and the other eye is displaced inferiorly with corresponding torsional movement in order to keep the eyes aligned along the horizon (17, 22). The emergence of pendular SSN could reflect a regression to an older optokinetic system of our evolutionary predecessors and corroborates current understanding of the neurologic mechanism for infantile nystagmus (17).

In contrast, jerky SSN is typically documented in patients with focal intrinsic lesions of the midbrain involving the INC or its afferent central graviceptive semicircular canal and/or otolithic projections from the vestibular nuclei (2). One widely accepted theory is that this results in an imbalance in vestibular input from the superior semicircular canals on both sides (3, 23, 24). Previously reported lesions include infarction, cavernoma, hypothalamic hamartoma and multiple sclerosis of the INC or along its afferent pathways in the mLF or medulla. (3, 25-28). Unlike pendular SSN, visual impairment is often absent in these patients and vestibular symptoms are more pronounced. Since the INC also has efferent projections to the cervical spinal cord, lesions may also cause a contraversive ocular tilt reaction, a type of postural synkinesis comprising of a head tilt to the contralateral side, ipsilateral hypertropia and ocular counter-~~rolling~~rolling (3, 23, 28, 29).

In summary, both forms of SSN are related to the impairment of vestibular responses initiated to maintain gaze stability during head rotation. Pendular SSN is associated with miscalibration of retinal error signals (compromise of the

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visuovestibular adaptive mechanism) and jerky SSN results from an imbalance of afferent vestibular signals to the INC (2). Their clinical presentations and underlying causes are distinct (Table 1). This case supports the concept that pendular SSN is a result of a double-hit involving a suprasellar lesion compressing against the optic chiasm leading to bitemporal hemianopia as well as the MTN leading to a disinhibited VOR.

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FIGURE LEGEND

Figure 1 Contrast T1-weighted MRI images showing an enhancing sellar mass with suprasellar extension compressing against the optic chiasm superiorly and the ventral midbrain (interpeduncular region) posteriorly (a: axial; b: sagittal; c: coronal)

Figure 2 Proposed pathways involved in the pathophysiology of pendular SSN

Double-hit hypothesis (compromise of the visuovestibular adaptive mechanism for the VOR): First hit: Compression of the chiasm (CHM) causes loss of bilateral temporal visual fields and retinal error miscalibration of the VOR leading to nystagmus in the roll plane. Second hit: Compression of the medial terminal nucleus (MTN) causes interruption of retinal error signals in the pitch plane: a) interruption of inhibitory afferent GABAergic neurons to the the interstitial nucleus of Cajal (INC) with subsequent vertical (pitch plane) and torsional (roll plane) nystagmus as exhibited in previous INC stimulation studies; and b) disinhibition of the VOR due to decreased cerebellar Purkinje fibers inhibitory signaling to the vestibular nuclei (VN). Abbreviations: AOS, accessory optic system; CHM, chiasm; ICN, interstitial nucleus

of Cajal; ION, inferior olivary nucleus; MTN, medial terminal nucleus; VN, vestibular nucleus; VOR, vestibulo-ocular reflex; III, oculomotor nerve nucleus, IV, trochlear nerve nucleus; VI, abducens nerve nucleus (adapted from Simpson et al (16)).

Figure 3. Anatomical location of the AOS terminal nuclei in the midbrain at the level of the superior colliculus

The MTN is part of the AOS located at the ventral midbrain. A large suprasellar tumor (e.g. a giant pituitary macroadenoma, dotted circle) may cause selective compression of the MTN sparing more dorsally located nuclei such as the INC, lateral terminal nuclei and dorsal terminal nuclei. The MTN conveys vertical plane retinal error signals and interruption of this pathway may cause miscalibration of the VOR in this plane. Abbreviations: AOS, accessory optic system; CN III, oculomotor nerve nucleus; DTN; dorsal terminal nucleus; INC, interstitial nucleus of Cajal; LTN; lateral terminal nucleus; MGB, medial geniculate body; mLF; medial longitudinal fasciculus; MTN, medial terminal nucleus; NOT, nucleus of the optic tract (adapted from Simpson et al (16)).

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Case Presentation

A 55-year-old Chinese female was admitted for progressive drowsiness and headache for one month. Three months prior to admission, she experienced oscillopsia and blurring of vision. On admission, the patient was alert with reduced bilateral visual acuity to 6/60 with bitemporal hemianopia. Fundoscopy showed bilateral band optic atrophy compatible with a chiasmatic or tract lesion. The most striking feature was the presence of pendular-waveform seesaw nystagmus characterized by elevation with incyclotorsion in one eye and depression with excyclotorsion (counter-clockwise torsion) of the fellow eye in all gaze positions (see video). The vertical and rotatory oscillations continuously alternated with each eye

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To elucidate the pathophysiology behind the dissociated vertical oscillations (in the pitch plane) that are the hallmark of pendular SSN, further understanding of AOS anatomy is required (14, 17, 19). Three paired AOS terminal midbrain nuclei receive visual signals from the contralateral retina through fibers of the accessory optic tract that are then relayed to the ipsilateral ION (14-16, 19). Rabbit electrical microstimulation studies have revealed that each pair of AOS terminal nuclei processes visual information regarding one of three cardinal rotational axes (14). In particular, the medial terminal nucleus (MTN) processes retinal error signals in the pitch plane (14, 15). The MTN is anatomically located at the ventral midbrain, bordered laterally by the cerebral peduncle and in close proximity to the interpeduncular cistern (19). Of the three terminal nuclei of the AOS, the MTN is the most vulnerable to anterior compression by large suprasellar lesions as suggested by our case (Figures 1 and 2). The consequence of selective compression of the MTN could result in a lack of transmission of retinal frame shift error signals in the pitch plane leading to vertical nystagmus. The sparing of the more posteriorly located dorsal and lateral terminal nuclei at the pretectal region may explain why pendular SSN lacks a horizontal movement component.

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Although an elucidation for the presence of the 180^{o} out-of-phase dissociated vertical eye movement observed in pendular SSN is lacking, a phylogenetic theory has been suggested. Deregulation of the AOS with subsequent disinhibition of the INC could represent an unmasking of an atavistic VOR pathway mediating vertical eye movement observed in lateral-eyed animals (17). Lateral-eyed animals (in contrast to frontal in humans) normally have dissociated binocular vision, i.e. when the head is tilted in the roll plane, one eye is turned superiorly and the other eye is displaced inferiorly with corresponding torsional movement in order to keep

the eyes aligned along the horizon (17, 22). The emergence of pendular SSN could reflect a regression to an older optokinetic system of our evolutionary predecessors and corroborates current understanding of the neurologic mechanism for infantile nystagmus (17).

In contrast, jerky SSN is typically documented in patients with focal intrinsic lesions of the midbrain involving the INC or its afferent central graviceptive semicircular canal and/or otolithic projections from the vestibular nuclei (2). One widely accepted theory is that this results in an imbalance in vestibular input from the superior semicircular canals on both sides (3, 23, 24). Previously reported lesions include infarction, cavernoma, hypothalamic hamartoma and multiple sclerosis of the INC or along its afferent pathways in the mLF or medulla. (3, 25-28). Unlike pendular SSN, visual impairment is often absent in these patients and vestibular symptoms are more pronounced. Since the INC also has efferent projections to the cervical spinal cord, lesions may also cause a contraversive ocular tilt reaction, a type of postural synkinesis comprising of a head tilt to the contralateral side, ipsilateral hypertropia and ocular counter-rolling (3, 23, 28, 29).

In summary, both forms of SSN are related to the impairment of vestibular responses initiated to maintain gaze stability during head rotation. Pendular SSN is associated with miscalibration of retinal error signals (compromise of the visuovestibular adaptive mechanism) and jerky SSN results from an imbalance of afferent vestibular signals to the INC (2). Their clinical presentations and underlying causes are distinct (Table 1). This case supports the concept that

pendular SSN is a result of a double-hit involving a suprasellar lesion compressing against the optic chiasm leading to bitemporal hemianopia as well as the MTN leading to a disinhibited VOR.

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FIGURE LEGEND

Figure 1 Contrast T1-weighted MRI images showing an enhancing sellar mass with suprasellar extension compressing against the optic chiasm superiorly and the ventral midbrain (interpeduncular region) posteriorly (a: axial; b: sagittal; c: coronal)

Figure 2 Proposed pathways involved in the pathophysiology of pendular SSN

Double-hit hypothesis (compromise of the visuovestibular adaptive mechanism for the VOR): First hit: Compression of the chiasm (CHM) causes loss of bilateral temporal visual fields and retinal error miscalibration of the VOR leading to nystagmus in the roll plane. Second hit: Compression of the medial terminal nucleus (MTN) causes interruption of retinal error signals in the pitch plane: a) interruption of inhibitory afferent GABAergic neurons to the the interstitial nucleus of Cajal (INC) with subsequent vertical (pitch plane) and torsional (roll plane) nystagmus as exhibited in previous INC stimulation studies; and b) disinhibition of the VOR due to decreased cerebellar Purkinje fibers inhibitory signaling to the vestibular nuclei (VN). Abbreviations: AOS, accessory optic system; CHM, chiasm; ICN, interstitial nucleus of Cajal; ION, inferior olivary nucleus; MTN, medial terminal nucleus; VN, vestibular nucleus; VOR, vestibulo-ocular reflex; III, oculomotor nerve nucleus, IV, trochlear nerve nucleus; VI, abducens nerve nucleus (adapted from Simpson et al (16)).

Figure 3. Anatomical location of the AOS terminal nuclei in the midbrain at the level of the superior colliculus

The MTN is part of the AOS located at the ventral midbrain. A large suprasellar tumor (e.g. a giant pituitary macroadenoma, dotted circle) may cause selective compression of the MTN sparing more dorsally located nuclei such as the INC, lateral terminal nuclei and dorsal terminal nuclei. The MTN conveys vertical plane retinal error signals and interruption of this pathway may cause miscalibration of the VOR in this plane. Abbreviations: AOS, accessory optic system; CN III, oculomotor nerve nucleus; DTN; dorsal terminal nucleus; INC, interstitial nucleus of Cajal; LTN; lateral terminal nucleus; MGB, medial geniculate body; mLF; medial longitudinal fasciculus; MTN, medial terminal nucleus; NOT, nucleus of the optic tract (adapted from Simpson et al (16)).

Figure 1

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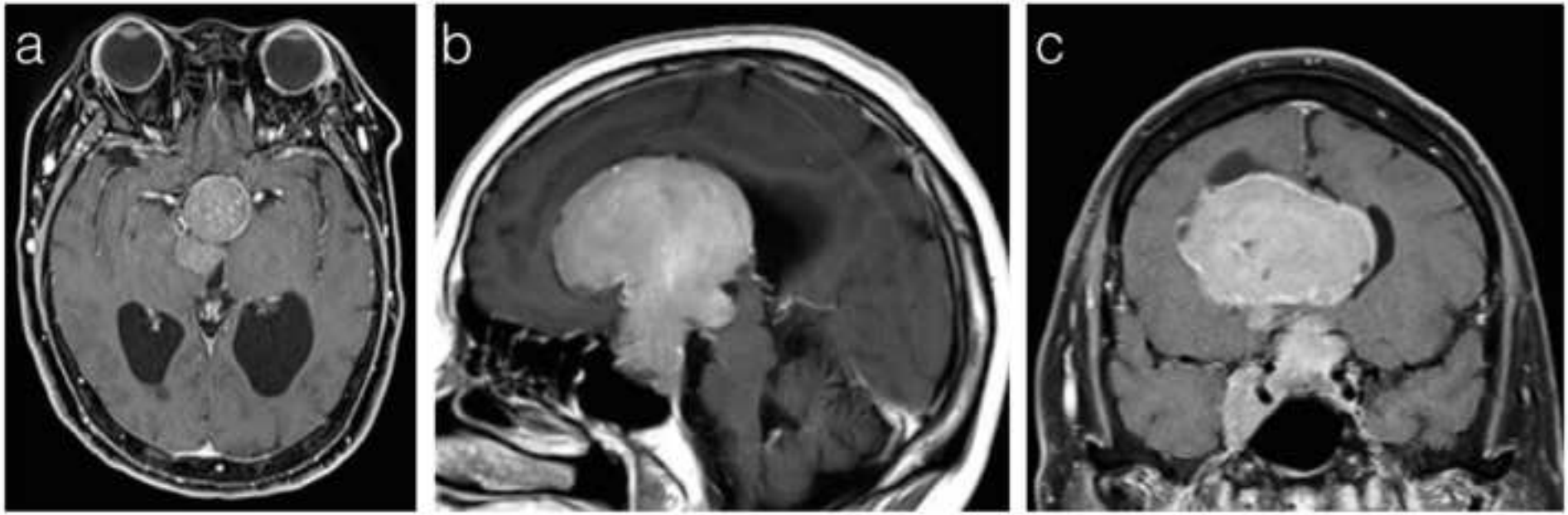

Figure 2

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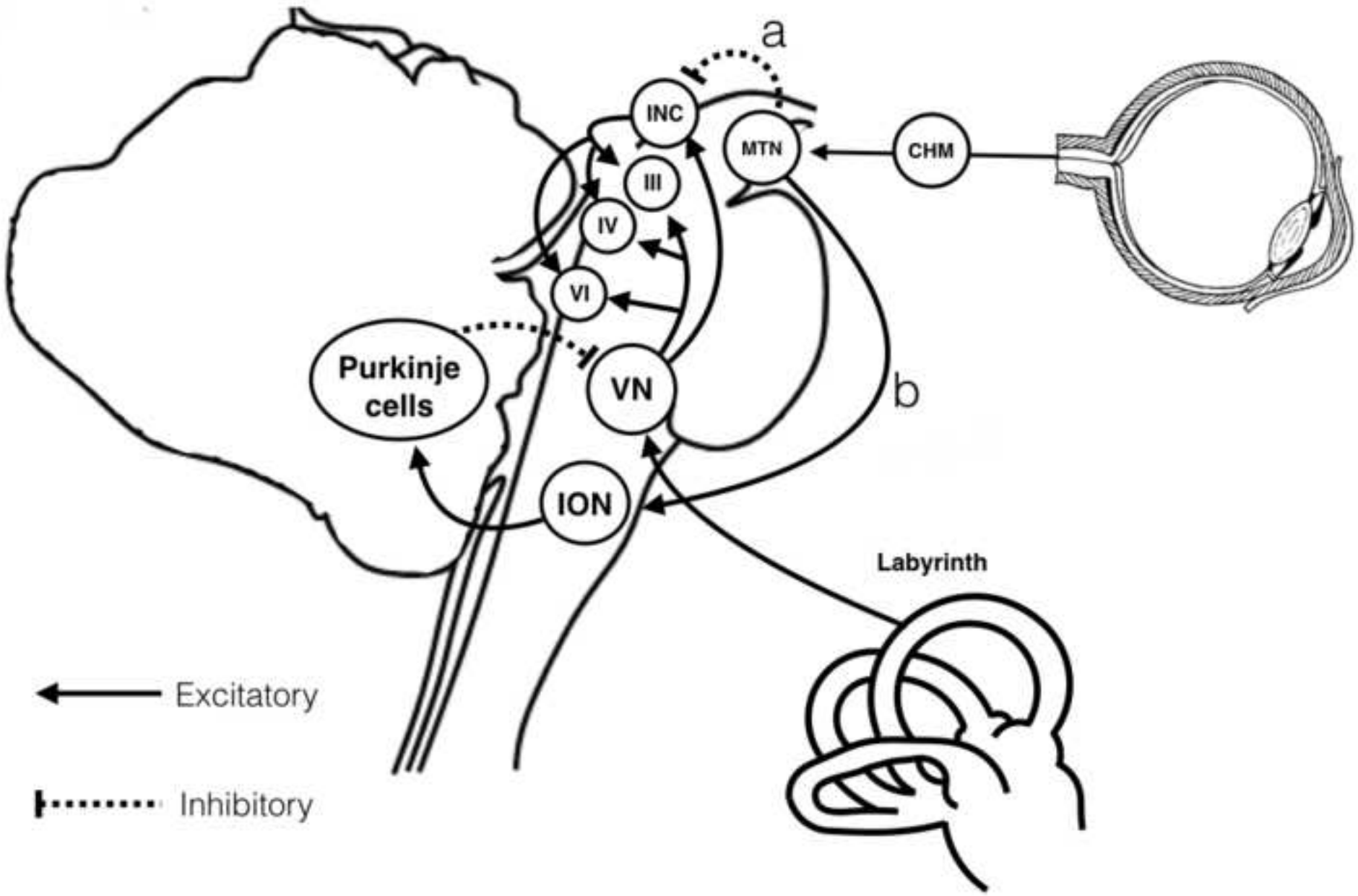

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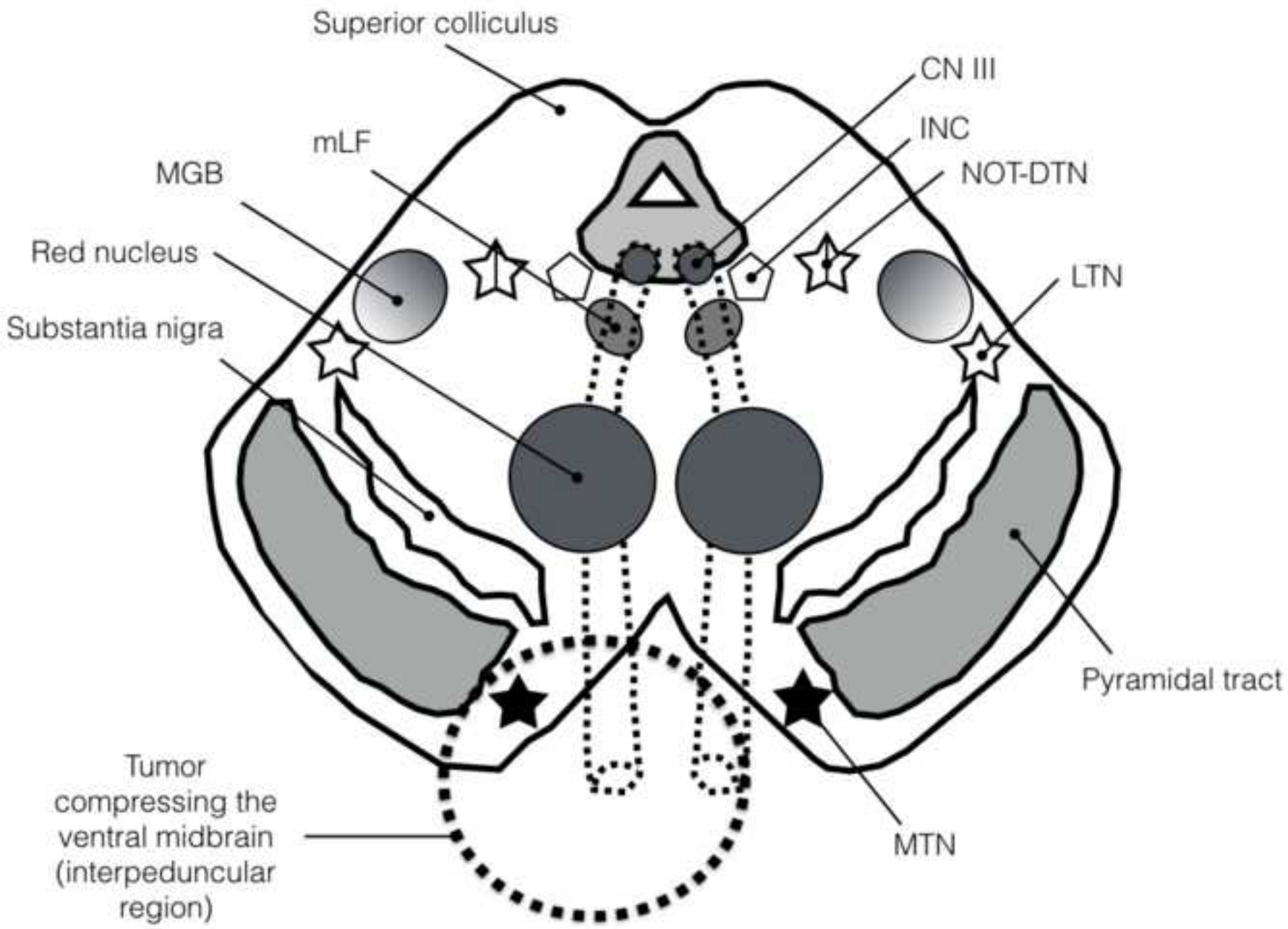

Table 1. Characteristics of the two forms of seesaw nystagmus

	Pendular SSN	Jerky SSN
Visual impairment	Yes	No
Nature nystagmus	SSN (torsion speed similar in each half cycle)	Hemi-SSN (fast and slow phases for each half-cycle)
Associated localizing signs	Bitemporal hemianopia (chiasm)	Ocular tilt reaction (INC) INO (mLF) Vestibular signs
Common etiology	Parasellar tumors	Infarct
Side of lesion	Midline	Unilateral (quick phase ipsilateral to lesion)

Abbreviations: SSN, seesaw nystagmus; INC, interstitial nucleus of Cajal; INO, internuclear ophthalmoplegia; mLF, medial longitudinal fasciculus

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Supplemental Video File

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